Hantavirus Infection in Children in Argentina

Clinical hantavirus infection was diagnosed in five Argentine children ages 5 to 11 years by immunoglobulin M (IgM)- capture enzyme-linked immunosorbent assay using Sin Nombre virus (SNV) antigens. Death in three of the children was associated with absence of detectable IgG to SNV antigens. An additional two cases in healthy children were studied: one, a breast-fed 15-month-old whose mother died of suspected hantavirus pulmonary syndrome (HPS) 8 months previously, had hantavirus IgG (≥ 1:6400); a second, whose mother survived HPS during month three of pregnancy, apparently had maternal antibodies no longer detectable 1 year after birth.

In May 1993, a new hantaviral illness, hantavirus pulmonary syndrome (HPS), was recognized in the southwestern region of the United States (1). HPS is a viral zoonosis characterized by a febrile prodrome in young, healthy adults; the disease progresses to respiratory failure with the clinical picture of adult respiratory distress syndrome (ARDS). The striking pulmonary involvement differentiates HPS from a previously described hantaviral disease known as hemorrhagic fever with renal syndrome.

In the first 100 HPS cases in the United States, the average age was 34.9 years (range 11 to 69); eight cases were in children or adolescents under 16 years of age (2). In Argentina, from 1987 to July 1997, 114 cases were diagnosed in three areas of the country where several strains of new world hantaviruses are known to cause HPS diseases (3,4). Before 1995, no cases were detected in Argentine children under 12 years of age. Ten cases were reported among adolescents (13 to 19 years) with a case-fatality rate of 30% (Instituto Nacional de Enfermedades Virales Humanas, [INEVH], unpub. data).

The initial case definition referred to ARDS and included adults and young adults (5) as the affected population. The lack of HPS cases among children in the original outbreaks led to a circulating hypothesis that children were not at risk or were at a very low risk for HPS. Another hypothesis was that children were protected from pulmonary involvement, perhaps by immune system immaturity or a lack of other risk factors (such as cigarette smoking) for lung injury.

In this report we describe five cases in children; in all of them the etiologic diagnosis was established by the presence of immunoglobulin M (IgM) antibody to Sin Nombre virus (SNV) antigens. Serologic results for two of the children were also positive for SNV IgG antibody. Serum samples were tested for IgM and IgG antibodies to SNV by enzyme-linked immunosorbent assay (ELISA) (6). An ELISA titer greater than or equal to 1:400 was considered positive (Table 1).

Patient 1 was identified during the study of the first outbreak in southern Argentina in 1995 (5). Four patients in this outbreak were from the same family. During interviews of the family members, we found that a 9-year-old boy had a febrile disease without respiratory involvement, beginning on April 19. Serology performed on May 3, 14 days after the onset of symptoms, demonstrated IgM and IgG antibodies to SNV antigens.

Table 1. Hantavirus infection in children, Argentina, 1995–1997

				Serology[a] Date			
Case	Sex	Age (yrs)	Date of onset	IgM IgG	Area[b]	Outcome
1	M	9	4-19-95	5-3-95 >6400 1600	South	Alive
2	F	5	3-21-97	3-23-97 >6400 Neg	North	Dead
3	M	9	3-30-97	4-3-97 1600 400	North	Alive
4	F	11	4-14-97	4-16-97 1600 Neg	North	Dead
5	M	5	4-27-97	4-28-97 1600 Neg	Central	Dead

[a]Titer expressed as the reciprocal of the serum dilution reactive in enzyme-linked immunosorbent assay.
[b]Area of origin in Argentina.

The other four cases in children were identified during routine surveillance. From 1995 to 1997, samples from 25 children (ages 3 months to 12 years; mean = 5.8 years) were sent to INEVH for diagnosis. Table 2 summarizes the main clinical and laboratory findings. None of the children had renal failure; patient 2 had uremia of 0.30 g/l, and patient 4 had a serum creatinine level of 1.40 g/l. All patients who later died received supplemental oxygen as part of their treatment.

Two special situations involving children arose during the study of the first cases of HPS in El Bolsón in 1995. 1) A woman belonging to the family of patient 1 contracted HPS during the first quarter of pregnancy. She had a febrile syndrome, without respiratory failure; chest X-rays showed bilateral interstitial infiltrates. Serologic tests showed both SNV IgM (≥ 1:6400) and IgG (≥ 1:6400) on April 22, 1995, 8 days after the onset of symptoms. She delivered a healthy infant in October 1995. A sample of the newborn's cord blood was positive for SNV IgG (≥ 1:6400) and negative for SNV IgM. A serum sample drawn from the mother at the same time had a SNV IgG titer ≥ 1:6400 and was negative for SNV IgM. A second serum sample, taken from the baby a year later during November 1996, had no detectable SNV IgG or IgM. 2) During a retrospective search for cases fulfilling the HPS case definition, a woman who died of ARDS in September 1994 was considered to have a possible case. No serum samples or autopsy tissues were available to make an etiologic diagnosis. Before dying, this woman breast-fed a 7-month-old baby; when tested for antibodies 8 months later in May 1995 at 15 months of age, the baby had SNV IgG (≥ 1:6400) and no detectable SNV IgM antibodies. A second serologic sample, collected 18 months later in November 1996, still had SNV IgG antibodies, with a similar titer. Both babies have continued to develop normally as of October 1997.

A case similar to that of patient 1 was detected in New Mexico in June 1993 (7) in the course of the investigation of a fatal HPS case. In this case, the patient also had a mild clinical course that did not meet the surveillance case definition for HPS. This case definition (revised 9/96) is as follows: "a febrile illness characterized by bilateral diffuse interstitial edema that may radiographically resemble ARDS, with respiratory compromise requiring supplemental oxygen, developing within 72 hours of hospitalization, and occurring in a previously healthy person; or an unexplained respiratory illness resulting in death, with an autopsy examination demonstrating noncardiogenic pulmonary edema without an identifiable cause" (8).

Our remaining four cases were sporadic, in persons without previous contact with other HPS patients, and were suspected because their clinical symptoms were typical of HPS. Results of serologic testing with SNV antigens of the household contacts in cases 2 and 5 (five persons

Table 2. Laboratory results and clinical features of children with hantavirus infection, Argentina, 1995–1997

Tests and features	Case 1	2	3	4	5
Leukocytes (/mm^3)	9,200	27,000	12,800	10,600	69,200
Hematocrit (%)	44	66	43	55	53
Thrombocytes (/mm^3)	ND[a]	266,000	200,000	97,000	ND
Sedimentation rate (mm/hr)	ND	4	28	8	1
GOT/GPT[b]	ND	Increased	Increased	Increased	Increased (mild)
Chest X-ray	HI[c]	DII[d]	DII	DII	DII
Respiratory symptoms	None	Distress	Slight dyspnea	Tachypnea, clinical and X-ray disassociation, hypoventilation	Acute respiratory insufficiency

[a]ND: Not done.
[b]GOT/GPT: Glutamic oxalacetic transaminase/Glutamic pyruvic transaminase.
[c]HI: Hilar indistinctness.
[d]DII: Diffuse interstitial infiltrate.

each) were negative. The clinical, radiologic, and laboratory findings were similar in children and in adults; severely ill patients had greater variation in laboratory values than mild cases, and in fatal cases, only SNV IgM was present.

The case-fatality rate in this series was 60%, but the small number of cases does not permit conclusions. In previously reported cases in adolescents 13 to 19 years of age, the case-fatality rate was 30%.

These cases originated in the three areas where the illness is endemic in Argentina. This is an important point because an unusual case of HPS in southern Argentina, with the possibility of person-to-person transmission, had been reported (9,10). Patient 1 and the baby that was breast-feeding when the mother died of suspected HPS could be further instances of person-to-person transmission.

A case of hemorrhagic fever with renal syndrome and pregnancy was reported in 1992 (11); the dynamics of serum antibody persistence were similar to those found in the one instance where we believe antibody was passively transferred from mother to baby. These results indicate that HPS should be considered in the differential diagnosis of respiratory distress or atypical bilateral pneumonia in children, at least in areas where these diseases have been confirmed. Mild disease should be considered too, especially in contacts of HPS patients and in younger age groups.

Our findings also suggest the transfer of passive antibodies from mother to fetus (without fetal infection) and the possibility of transmission of infection by maternal breast feeding.

Noemí C. Pini,* Amanda Resa,† Gladys del Jesús Laime,‡ Gustavo Lecot,¶ Thomas G. Ksiazek,§ Silvana Levis,* and Delia A. Enria*

*Instituto Nacional de Enfermedades Virales Humanas "Dr. Julio I Maiztegui," Pergamino, Argentina; †Hospital de El Bolsón, Río Negro, Argentina; ‡Hospital de Orán, Salta, Argentina; ¶Hospital de Olavarría, Buenos Aires, Argentina; and §Centers for Disease Control and Prevention, Atlanta, Georgia, USA

References

1. Centers for Disease Control and Prevention. Outbreak of acute illness: southwestern United States, 1993. MMWR Morb Mortal Wkly Rep 1993;42:421-4.
2. Khan AS, Khabbaz RF, Armstrong LR, Holman RC, Bauer SP, Graber J, et al. Hantavirus pulmonary syndrome: the first 100 US Cases. J Infect Dis 1996;173:1297-303.
3. Parisi MN, Enria DA, Pini NC, Sabattini M. Detección retrospectiva de infecciones clínicas por hantavirus en la Argentina. Medicina (B Aires) 1996;56:1-13.
4. Levis SC, Briggiler AM, Cacase M, Peters CJ, Ksiazek TG, Cortés J, et al. Emergence of hantavirus pulmonary syndrome in Argentina [abstract]. Am J Trop Med Hyg 1995;53:233.
5. Hughes JM, Peters CJ, Cohen ML, Mahy BWJ. Hantavirus pulmonary syndrome: an emerging infectious disease. Science 1993;262:850-1.
6. Ksiazek TG, Peters CJ, Rollin PE, Zaki S, Nichol S, Spiropoulou C, et al. Identification of a new North American hantavirus that causes acute pulmonary insufficiency. Am J Trop Med Hyg 1995;52:117-23.
7. Armstrong LR, Bryan RT, Sarisky J, Khan AS, Rowe T, Ettestad PJ, et al. Mild hantavirus disease caused by Sin Nombre virus in a four-year-old-child. Pediatr Infect Dis J 1995;12:1108-10.
8. Centers for Disease Control and Prevention. Case definitions for infectious conditions under public health surveillance. MMWR Morb Mortal Wkly Rep 1997;46:16.
9. Enria D, Padula P, Segura EL, Pini N, Edelstein A, Riva Posse C, Weissenbacher MC. Hantavirus pulmonary syndrome in Argentina. Possibility of person-to-person transmission. Medicina (B Aires) 1996;56:709-11.
10. Wells RM, Sosa Estani S, Yadon ZE, Enria DA, Padula P, Pini N, et al. An unusual hantavirus outbreak in southern Argentina: person-to-person transmission? Emerg Infect Dis 1997;2:171-4.
11. Silberberg L, Rollin PE, Keourani G, Courdrier D. Haemorrhagic fever with renal syndrome and pregnancy: a case report. Trans R Soc Trop Med Hyg 1993;87:65.